REMARKS

Claims 76-81 and 101-119 are pending in the application and stand rejected. Withdrawn claims 109-119 have been cancelled. In response to the Office Action, claims 76, 79, and 101 have been amended. Support can be found in various parts of the specification, for example, ¶2 on page 15 discussing new proteins in the next generation library, ¶5 on page 15 discussing the updated training set, and ¶3 on page 81 describing various forms of tangible media, such as a hard disk, floppy disk, magnetic tape, and others. New claims 120-122 have been added. Support can be found on page 13, ¶4, and page 14, ¶1. No new matter has been introduced by these non-limiting amendments and new claims. It is not the Applicants' intent to surrender any equivalents because of the amendments or arguments made herein. Accordingly, claims 76-81 and 101-122 remain pending. Reexamination and reconsideration of the application, as amended, are respectfully requested.

The Provisional Double Patenting Rejection

Claims 76-81 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 7-9, and 14 of copending Application No. 11/706,034 in view of Hellberg et al. Applicants will consider this rejection again when an indication of allowable subject matter is made in either the present application or Application No. 11/706,034 (Attorney Docket MXGNP004X2D1). Applicants note that Application No. 11/706,034 was filed after the present application.

The Rejection under 35 USC 101

Claims 79-81 were rejected under 35 USC 101 as being directed to non-statutory subject matter. The Office Action stated that these claims are "drawn to a carrier wave." To expedite prosecution independent claim 79 has been amended to recite "a tangible machine readable medium." The support can be found in ¶3 on page 81 of the specification, which recites:

> Examples of computer-readable media include, but are not limited to, magnetic media such as hard disks, floppy disks, magnetic tape; optical media such as CD-ROM devices and holographic devices; magneto-optical media; semiconductor memory devices, and hardware devices that are specially configured to store and perform program instructions, such as read-only memory devices (ROM) and random access memory (RAM), and sometimes application-specific integrated circuits (ASICs), programmable logic devices (PLDs)...

This extensive list of physical machine readable media provides a legally sufficient written description of "tangible machine readable" media. Withdrawal of the rejection under 35 USC 101 is respectfully requested.

The Rejection under 35 USC 112, second paragraph

Claims 76-78 and 101-108 were rejected under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. The Office requested that Applicants clarify "protein variants" in operation (e) of claim 76. According to the Office Action, it was not clear whether the "protein variants" in this operation refer to the variants in operation (a) or to the protein variants generated in operation (d). Claim 76 has been amended to recite: "(e) generating a new protein variant library containing one or more ~~of the~~ new protein variants." In the amended form, claim 76 clearly distinguishes the "new protein variants" from the "variants" in operation (a). The "new protein variants" are included in the new protein variant library that is generated in operation (e) and is based on the identified amino acid residues in operation (d). The "new protein variants" of operation (e) are different from the "variants" of operation (a) that are a part of the training set.

The Office also indicated that it was not clear whether "using **the new** computational algorithmic sequence activity model" (emphasis added) in operation (g) referred to "**a new** computational algorithmic sequence activity model" (emphasis added) in operation (f) or "**a** computational algorithmic sequence activity model" (emphasis added) in operation (b). Applicants respectfully traverse. Claim 76 recites two different activity models each separately identified with its own distinct name. One is identified as "**a** computational algorithmic sequence activity model" in operations (b) and (c). Another one is identified as "**a new** computational algorithmic sequence activity model" in operations (e) and (f). Two different names are used for the two different activity models. Proper antecedent basis has been used in operations (b) and (c) and in operations (e) and (f). Therefore, Applicants respectfully submit that it is clear that "**the new** computational algorithmic sequence activity model" in operation (g) only refers to "a new ... model" in operation (f) and not to "a ... model" in operation (b).

Applicants respectfully submit that claims 76-78 and 101-108 now meet the requirements of 35 USC 112, second paragraph, and respectfully request withdrawal of the rejection.

The Rejection under 35 USC 103(a)

Claims 76-81 and 101-108 were rejected under 35 USC 103(a) as being unpatentable over Hellberg et al. (J. Med. Chem., vol. 30 (1987) pgs. 1126-1135) in view of newly cited Schellenberger et al. (US Patent Pub. No. 2002/0155460). The Office acknowledged that Hellberg does not teach at least element (f) of claims 76, which recites:

assaying the new protein variant library to provide an updated training set comprising sequence and activity information for members of the new protein variant library ~~used~~ to develop a new computational algorithmic sequence activity model

Independent claim 79 includes similar features. The Office then argued that Schellenberger teaches element (f) of claim 76 pointing to Schellenberger's paragraph [0099], which deals with characterization of libraries. Applicants respectfully traverse and submit that neither Schellenberger nor any other cited reference teach this element. Further, the combination of Hellberg and Schellenberger advocated in the Office Action would not lead a skilled artisan to the claimed invention. Withdrawal of the art-based rejection is respectfully requested.

Schellenberger describes a method for generating libraries of biological polymers. The reference points out that there is a need to increase a proportion of library members with desired activities (see paragraph [0010]) and proposes a method employing probabilities that certain individual residues will impact desired characteristics of biological molecules. The overall method includes: generating a probability matrix, setting a constraint vector, designing a substitution scheme based on the matrix and the vector, constructing a library based on the scheme, and finally characterizing the members of the library (see paragraph [0012]). The reference mentions in paragraph [0099] that the library information can be used to design an improved probability matrix and constraint vector for a next iteration of mutagenesis. However, because neither the probability matrix nor the constraint vector can be properly characterized as a computational algorithmic *sequence activity model*, Schellenberger does not teach element (f) of claim 76. Schellenberger's "model" is simply probability information specific to individual residues that are present in the probability matrix.

Specifically, Schellenberger's probability matrix contains probability estimates that "**a given residue**" will impact a desired activity in a biological polymer (see paragraph [0059], also cited in the Office Action in §9 on page 11). FIG. 1 illustrates an example of the matrix, where each row represents a residue position in a biological polymer and each column represents one type of residues (see paragraph [0060]). The matrix shows a probability estimate at the intersection of each row and column, illustrated as a vertical bar in FIG. 1. This estimate represents the probability that a polymer will have a desired activity if that particular residue (column value) is found in that position (row value) (see paragraph [0060]). This approach falls well short of a computational algorithmic sequence activity model that estimates activity for an entire sequence. Unlike a sequence activity model, Schellenberger's probability matrix simply considers the probability of a single residue at a single position and ignores other aspects of a sequence that collectively impact the activity of the sequence. Therefore, the probability matrix is not representative of a computational algorithmic sequence activity model.

Additionally, it is difficult to decipher the physical or mathematical basis for Schellenberger's probability matrix, as the reference does not clearly specify how its probability matrix is derived or what the individual numerical values of the probability matrix represent. Schellenberger's probability matrix and method of generating one are generally open-ended and ill-defined. Schellenberger does not provide sufficient description of the probability matrix to guide a skilled artisan to teachings of the claims. The reference briefly mentions in paragraph [0068] that a variety of different substitution matrices can be used as input for calculating a probability matrix. Schellenberger then generally points out in paragraph [0071] that an algorithm that determines a probability matrix can be desired or even required and that the development of such algorithm is within the skill in the art. Overall, Schellenberger's description provides, at best, only very limited guidance to those of skill in the art.

As indicated, Schellenberger's method employs a constraint vector, which is applied to the probability matrix in order to select mutations and respective positions to be included in the library. Schellenberger provides a few examples of constraint vectors: a correlation matrix (see [0073], a proximity-based method (see [0074] – [0078]), correlation in evolutionary data (see [0078]) and conservation indexes (see [0079]). FIG. 1 illustrates application of the constraint vector to the matrix. The reference indicates that the candidates for mutagenesis are only those positions in the matrix that have probability values higher than the corresponding values in the constraint vector. Essentially, the vector acts as a set of thresholds that provides minimum desired probabilities for each residue in each position. Applying the vector to the matrix simply limits the number of residues and positions for mutagenesis in order to generate "a library of a size which can be effectively screened for a desire property" (see paragraphs [0082]). Likewise, the constraint vector and a process of applying the vector to the matrix is not representative of a computational algorithmic sequence activity model. Nowhere does Schellenberger indicate that activities of new library members can be calculated from the constraint vector and/or the probability matrix.

Schellenberger then describes characterization of the identified library members (see paragraphs [0098] – [0102]). The Office argues that Schellenberger's paragraph [0099] teaches screening the library and using the screen information "to design an improved probability matrix and constraint vector (i.e. develop a new computational algorithmic sequence activity model)" (see ¶ 12, p. 12 of the Office Action). However, as indicated above, neither the matrix nor the vector (or its application to the matrix) constitutes a sequence activity model. Therefore, the Office improperly concluded that Schellenberger develops a new sequence activity model disclosure. Since Schellenberger does not teach a computational algorithmic sequence activity model, it can not teach developing such model based on activity information provided from assaying a library.

The Office noted that Schellenberger mentions QSAR techniques. Schellenberger identifies QSAR as an approach that "can be used for the libraries of the instant invention" (see paragraph [0104]) and for statistical analyses "to assign the degree to which individual mutations or combination of mutations contribute to the observed improvement of properties, and to identify which pairs or groups of amino acids interact with each other" (see paragraph [0105]). Beyond this, Schellenberger provides very little explanation of how QSAR techniques might be used with his overall methodology. There is no suggestion that a QSAR model could be an alternative to Schellenberger's probability matrix or constraint vector. There is nothing to suggest that Schellenberger's use of QSAR is pertinent to Hellberg or the claimed invention. Schellenberger simply states that QSAR could be used analyze libraries. Schellenberger likely uses QSAR to further characterize the assayed libraries.

Applicants also take issue with the Office's position that a skilled artisan would be motivated to combine Hellberg and Schellenberger. The Office Action cites Schellenberger's need to "systematically screen all possible permutations of a polymeric biological molecule" (see Schellenberger's background of the invention section). The Office also points out that Schellenberger mentions a QSAR method. However, this motivation to combine Hellberg's QSAR with Schellenberger's library optimization method does not lead to the claimed invention.

The fact that there is a need for a systemic screening of permutations is simply too general a motivation and would not in itself lead a skilled artisan to the claimed invention. Hellberg discloses a method for predicting activities of new peptide analogs using a computational methodology, such as QSAR (see Hellberg's Abstract, p. 1126). Schellenberger deals with narrowing library populations based on likelihood that individual residues will impact desired properties of library members. Even if there exists a legally sufficient rationale for combining the two references, the Office does not provide a rationale for selecting specific elements from one reference incorporating them with elements described in the other reference in a manner that suggests the claimed invention. For example, if one of skill were asked to combine Hellberg and Schellenberger in a manner that incorporates Hellberg's QSAR tool in Schellenberger's scheme, it seems that one of skill might logically use Hellberg's QSAR in place of or in addition to Schellenberger's library assay techniques, rather than in place of Schellenberger's library selection tools (the probability matrix and constraint vector). The Office does not explain how Hellberg's results of QSAR study comparing observed and calculated activities in Hellberg's FIG. 3 (argued to disclose element (d) of claim 76) might supplement or replace Schellenberger's probability matrix and constraint vector (argued to disclose element (e) of claim 76). Further, it is not clear from the Office's argument where Hellberg identifies one or more nucleotides and how any such identified nucleotides might be used with Schellenberger's probability matrix and constraint vector to generate a new protein variant library. Applicants respectfully request that the Office provide a rationale for selecting

particular features from the cited references and a rationale for combining them in a manner leading to the claimed invention.

Overall, not only do the cited references fail to teach every element of independent claim 76 but there is also no legally sufficient motivation to combine the references in the manner claimed.

To advance prosecution, Applicants have amended the independent claims to recite that assaying the new protein variant library provides a training set comprising sequence and activity data to develop a new sequence activity model. Nowhere does Schellenberger suggest that such assay results from a library should be used as a training set to generate a *new* model. Schellenberger's examples involve, at most, use of assay data to refine or improve existing probability matrixes or constraint vectors. Further, there is no suggestion that sequence-activity data be used as a training set for refining or developing a new model.

Claims 77, 78, and 101-108 are dependent on claim 76 and are therefore likewise patentable over the cited art. Claims 79-81 are patentable over the cited art for similar reasons. Applicants respectfully note that claims 79-81 are directed to computer program products. However, the data used by certain of the recited instructions (e.g., the code of elements (a) and (g)) is derived from physical compounds as recited in claim 76. Withdrawal of all art rejections is respectfully requested.

Conclusion

Applicants believe that all pending claims are allowable and respectfully request a Notice of Allowance for this application from the Examiner. Should the Examiner believe that a telephone conference would expedite the prosecution of this application, the undersigned can be reached at the telephone number set out below.

If any fees are due in connection with the filing this Response, the Commissioner is hereby authorized to charge such fees to Deposit Account 504480 (Order No. MXGNP004X1).

Respectfully submitted,
WEAVER AUSTIN VILLENEUVE & SAMPSON LLP

/ Jeffrey K. Weaver/
Jeffrey K. Weaver
Registration No. 31,314

/ Vladimir Y. Gusev/
Vladimir Y. Gusev
Reg. 59,689

510-663-1100
P.O. Box 70250
Oakland, CA 94612-0250